REMARKS

The specification has been amended to correct the spelling of "ceftazidime," "cycloheximide" and "phosphomycin."

Claim 1 has been amended to recite that the selective growth medium comprises nitrofurantoin. Support for this amendment is found in Claim 2 as originally recited.

Claim 2 has been amended to remove nitrofurantoin from the recited Markush group.

Claim 6 has been amended to recite that the lithium chloride is present in a concentration of from about 1 g/L to about 5 g/L. Support for the amendment is found in the combination of Claim 5 as originally filed and page 4, lines 3-4 of the specification as filed.

Claim 7 has been amended to depend from Claim 1.

Claim 9 has been amended to recite that the medium comprises cycloheximide and that the recited components are present in concentrations effective to enhance growth of *Listeria spp.* Support for the amendment is found in the specification at page 4, lines 18-20 and page 5, line 2.

Restricted Claim 14 has been canceled herein without prejudice to its merit. Applicant reserves the right to pursue Claim 14 in continuing applications.

Claim 15 has been amended to incorporate the content of now-canceled Claim 14, from which Claim 15 formerly depended.

Restricted Claims 16-24 and 28 have been amended to depend from 15 and are now directed to the elected invention.

Claims 17-21 have been reworded to be consistent with Claim 15 as amended.

Claims 2, 12, 25, and 31 have been amended to correct the spelling of "ceftazidime." Claims 22 and 31 have been amended to correct the spelling of "cycloheximide."

Claims 32-34 have been added. Claims 32-34 depend from Claims 1, 15, and 31, respectively, and recite that the medium is substantially devoid of acriflavin. Claim 32 further recites that the medium further includes cycloheximide. Support for the claims is found in the specification at page 3, lines 29-30 and page 5, line 2.

Claims 1-13 and 15-31 are pending and currently under consideration.

Rejection of Claim 6 under 35 U.S.C. §112, Second Paragraph

Claim 6 has been rejected as indefinite for reciting an open-ended range. This rejection has been overcome by amending Claim 6 to recite a range of from about 1 g/L to about 5 g/L.

Withdrawal of this rejection is requested.

Rejection of Claims 1, 4-6, and 9 under 35 U.S.C. §102(b) over Lee et al.

This rejection as applied to Claims 1 and 4-6 has been overcome by amendment of Claim 1. Claim 1 has been amended to recite that the selective growth medium comprises nitrofurantoin. Lee et al. do not teach a growth medium comprising nitrofurantoin. Therefore, Claim 1 and Claims 4-6 are not anticipated by Lee et al.

This rejection as applied to Claim 9 has been overcome by amendment of the claim. Claim 9 has been amended to recite that the selective growth medium comprises cycloheximide. Lee et al. do not teach a growth medium comprising cycloheximide. Therefore, Claim 9 is not anticipated by Lee et al.

Withdrawal of this rejection is requested.

Rejection of Claims 1, 4-6, and 9 under 35 U.S.C. §102(b) over Difco Manual

This rejection as applied to Claims 1 and 4-6 has been overcome by amendment of Claim 1. Claim 1 has been amended to recite that the selective growth medium comprises nitrofurantoin. Difco Manual does not teach a growth medium comprising nitrofurantoin. Therefore, Claim 1 and Claims 4-6 are not anticipated by Difco Manual.

This rejection as applied to Claim 9 has been overcome by amendment of the claim. Claim 9 recites a selective growth medium that is substantially devoid of acriflavin and has been amended to recite that the selective growth medium also comprises cycloheximide. Difco Manual does not teach a growth medium that comprises cycloheximide and is substantially devoid of acriflavin. For example, Difco Manual teaches an Oxford Antimicrobic Supplement that includes cycloheximide. However, this supplement also includes acriflavine (see page 365 of Difco Manual). Difco Manual does not otherwise teach any supplement or growth medium that includes cycloheximide. Therefore, Claim 9 is not anticipated by Difco Manual.

Withdrawal of this rejection is requested.

Rejection of Claims 1, 4-6, and 9 under 35 U.S.C. §102(b) over Neamatallah et al.

This rejection as applied to Claims 1 and 4-6 has been overcome by amendment of Claim 1. Claim 1 has been amended to recite that the selective growth medium comprises nitrofurantoin. Claims 1 and 4-6 as currently recited therefore require that the selective growth medium includes nitrofurantoin in a concentration such that the medium is effective to selectively inhibit non-*Listeria* organisms while enhancing growth of *Listeria spp.* Neamatallah et al. do not teach a growth medium comprising nitrofurantoin in any concentration that is effective to selectively inhibit non-*Listeria* organisms while enhancing growth of *Listeria spp.* For example, Neamatallah et al. test the sensitivity of *Listeria monocytogenes* to a variety of antibiotics in Oxford *Listeria* selective agar (Oxford formulation) (see Neamatallah et al. at paragraph spanning pages 230 and 231). The antibiotics tested include ampicillin, carbenicillin, cephalothin, colistin sulphate, cotrimoxazole, nalidixic acid, nitrofurantoin, penicillin G, sulphamethizole, and tetracycline. Of these, Neamatallah et al. report that *Listeria monocytogenes* was resistant only to colistin sulphate, nalidixic acid, and sulphamethizole (Neamatallah et al. at first paragraph under Results and Discussion on page 231). The medium including nitrofurantoin is not reported either to selectively inhibit non-*Listeria* organisms or to enhance growth of *Listeria spp.* To anticipate a claim under 35 U.S.C. §102, a prior art reference must not only teach each and every element of the claim, but the elements so taught must be arranged as required in the claim (MPEP §2131 and *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990)). Therefore, Claim 1 and Claims 4-6 are not anticipated by Neamatallah et al.

This rejection as applied to Claim 9 has been overcome by amendment of the claim. Claim 9 has been amended to recite that the selective growth medium comprises cycloheximide. Neamatallah et al. do not teach a growth medium comprising cycloheximide. Therefore, Claim 9 is not anticipated by Neamatallah et al.

Withdrawal of this rejection is requested.

Rejection of Claims 1-13, 15, 25-27, and 29-31 under 35 U.S.C. §103(a) over Lee et al., Difco Manual, and Neamatallah et al.

This rejection has been overcome, in part, by amendment of the claims and is, in part, traversed.

In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007), the Supreme Court reaffirmed that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 418. Rather, the court stated:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements **in the way the claimed new invention does**...because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known. (*Id.* at 418-419; emphasis added)

See also *id.* at 418 (requiring a determination of "whether there was an apparent reason to combine the known elements **in the fashion claimed** by the patent at issue") (emphasis added.) Ultimately, therefore, as the Federal Circuit court has stated, "[i]n determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.* 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted). In the present case, whether or not each ingredient was known independently in the prior art, the prior art does not provide teachings suggesting combining such ingredients in the way the claims recite.

Claim 1, for example, has been amended to recite the antibiotic nitrofurantoin. Claim 1 as amended now recites a selective growth medium specific for *Listeria spp.* comprising, in combination, lithium chloride and one or more antibiotics comprising nitrofurantoin or salts thereof in concentrations effective to selectively inhibit non-*Listeria* organisms while enhancing growth of *Listeria spp.* The prior art does not teach or suggest this combination of elements and limitations. Lee et al. and Difco Manual are completely silent regarding nitrofurantoin. Neamatallah et al. mention nitrofurantoin. However, Neamatallah et al. do not teach a concentration of nitrofurantoin effective to selectively inhibit non-*Listeria* organisms while enhancing growth of *Listeria spp.* In fact, Neamatallah et al. do not provide any suggestion whatsoever that nitrofurantoin can inhibit non-*Listeria* organisms while even **maintaining**, let

alone enhancing, growth of *Listeria spp.* In this manner, Neamatallah et al. do not provide any teachings to motivate including nitrofurantoin in a selective growth medium specific for *Listeria spp.*

Neamatallah et al. instead include teachings suggesting that nitrofurantoin is **not** suitable for a selective growth medium specific for *Listeria spp.* Neamatallah et al. assess the sensitivity of *Listeria monocytogenes* to nitrofurantoin in addition to many other compounds (Neamatallah et al. at paragraph spanning pages 230-231). Neamatallah et al. use in further experiments only those antibiotics to which *L. monocytogenes* show resistance: "Antimicrobial compounds, which demonstrated resistance to *L. monocytogenes*, were used to enhance selectivity" (Neamatallah et al. at page 231, left-hand column, section entitled "Evaluation of Bacteriological media"). Among all the compounds tested for resistance to *L. monocytogenes*, however, Neamatallah et al. teach that *L. monocytogenes* was resistant only to colistin sulphate, nalidixic acid, and sulphamethizole (Neamatallah at paragraph spanning pages 231 and 232). Consistent with their statement that only the compounds to which *L. monocytogenes* shows resistance were used to enhance selectivity, only colistin sulphate, nalidixic acid, and sulphamethizole were used in subsequent experiments to enhance selectivity (Neamatallah et al. at Table 2 and paragraph spanning pages 231 and 232). These experiments teach that that nitrofurantoin is not suitable for a selective growth medium specific for *Listeria spp.* because, as taught by Neamatallah et al., *L. monocytogenes* was not resistant to it.

In sum, Neamatallah et al. mention nitrofurantoin. However, in view of the standards set by *KSR*, it is not enough for obviousness to show that nitrofurantoin was known in the prior art. There must a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claims do. Neamatallah et al. do not provide any rationale for combining nitrofurantoin in a selective growth medium specific for *Listeria spp.* Therefore, Claims 1-8 are not obvious over Lee et al., Difco Manual, and Neamatallah et al.

Claim 9 has been amended to further recite cycloheximide in combination with lithium chloride, a growth enhancer of *Listeria spp.*, and antibiotics or salts thereof in a selective medium for *Listeria spp.* that is substantially devoid of acriflavin.

The prior art does not teach or suggest the combination of elements recited in Claim 9. Lee et al. and Neamatallah et al., for example, are completely silent regarding cycloheximide. Difco Manual describes cycloheximide but **only in combination with acriflavine** (see "Oxford Antimicrobic

Supplement" on page 365, left-hand column of Difco Manual). Difco Manual does not otherwise describe cycloheximide in a selective growth medium for *Listeria*. Furthermore, Difco Manual does not describe any properties of either cycloheximide or acriflavine that would prompt a practitioner in the art to include the former without the latter in a selective medium for *Listeria spp*. In view of *KSR*, it is not enough for establishing obviousness to show that cycloheximide has been included in a *Listeria* growth medium. Rather, there must be some teaching to suggest including cycloheximide in a manner recited in the claims, *i.e.*, in the absence of acriflavine. The combination of prior art references does not teach or suggest a *Listeria* growth medium that includes cycloheximide without acriflavine. Therefore, Claims 9-13 are not obvious over Lee et al., Difco Manual, and Neamatallah et al.

Claim 15 has been amended to incorporate the subject matter of Claim 14 as previously recited. Claim 15 now recites a *Listeria spp*.-selective medium comprising, in combination, cycloheximide, naladixic acid, ferric ammonium citrate, esculin, ceftazidime, phosphomycin, polymyxin E, lithium chloride, and nitrofurantoin in concentrations effective to promote growth of *Listeria spp.* and to inhibit growth of non-*Listeria* organisms.

The cited prior art does not teach or suggest a *Listeria*-selective medium comprising the combination of elements recited in Claim 15. As described above, only Neamatallah et al. even mention nitrofurantoin. However, Neamatallah et al. do not teach any reasons to combine nitrofurantoin in a *Listeria*-selective medium with the above-listed elements. Also as described above, only Difco Manual even mentions cycloheximide. However, Difco Manual does not teach combining cycloheximide with such antibiotics as naladixic acid, ceftazidime, polymyxin E, and nitrofurantoin.

It is not obvious to modify the teachings of the prior art references to combine the antibiotics in a manner recited in the claims. Neamatallah et al. teach that different combinations of antibiotics have unpredictable effects on *Listeria* growth. This is true even with antibiotics to which *Listeria* is apparently resistant. For example, Neamatallah et al. teach that *L. monocytogenes* is resistant to each of colistin sulphate, nalidixic acid, and sulphamethizole. However, an *L. monocytogenes* growth medium including sulphamethizole in combination with colistin sulphate and nalidixic acid reduced growth of the ATCC 19115 strain of *L. monocytogenes* by a full order of magnitude with respect to a combination of only colistin sulphate and nalidixic acid (Neamatallah et al. at Table 2). Thus, antibiotics to which *L. monocytogenes* is apparently resistant reduced growth of *L. monocytogenes* when combined together. In

view of this teaching, it is not obvious that combining cycloheximide, naladixic acid, ceftazidime, polymyxin E, and nitrofurantoin, in any concentration, would predictably inhibit growth of non-*Listeria* organisms while permitting promotion of growth of *Listeria spp.*

In view of the foregoing, Claims 15-30 are not obvious over Lee et al., Difco Manual, and Neamatallah et al.

This rejection as applied to Claim 31 is traversed. As described above with respect to Claim 15, the prior art does not provide any reason to combine nitrofurantoin in a *Listeria*-selective medium. The prior art also does not provide teachings to specifically suggest combining cycloheximide with naladixic acid, ceftazidime, polymyxin E, and nitrofurantoin. For these reasons alone, the particular combination of elements recited in Claim 31 is not obvious over Lee et al., Difco Manual, and Neamatallah et al.

In view of such differences between the medium recited in Claim 31 and those of the prior art, the Office has stated that "adjustment of ingredients and concentrations for optimization purposes identified as result effective variables cited in the references would have been prima facie obvious to a person having ordinary skill in the art" (Office Action dated April 5, 2010 at first paragraph on page 5). However, *KSR* established that for a particular combination of elements to be obvious, there must be "a finite number of identified, predictable solutions" (*KSR* at 1397). The number of possible solutions from the putative result effective variables taught in the prior art is a large, unwieldy number. Furthermore, the effectiveness of any particular combination is by no means predictable.

For example, the prior art teaches a total of at least 24 separate ingredients for *Listeria* media. These include:

> Bacto tryptose (10 g/L); bacto beef extract (3 g/L); sodium chloride (5 g/L); bacto agar (15 g/L); phenylethanol (2.5 g/L); bacto Columbia blood agar base (comprising pantone, bitone, and tryptic digest of beef heart) (39 g/L); bacto mannitol (10 g/L); bacto dextrose (0.5 g/L); phenol red (0.08 g/L); esculin (1 g/L); ferric ammonium citrate (0.5 g/L); lithium chloride (15 g/L); bacto agar (2 g/L); acriflavine (5 mg/L); cefotetan (2 mg/L); colistin sulfate (20 mg/L); colistin sulfate (10 mg/L); cycloheximide (400 mg/L); fosfomycin (10 mg/L); moxalactam (20 mg/L); polymyxin B sulfate (10 mg/L); ceftazidime (40 mg/L); sulphamethizole (200 mg/L); phenylethanol; and glycine anhydride.

Importantly, the prior art teaches that not all of these possible ingredients can be predictably interchanged or combined in a beneficial manner. For example, Lee et al. teach that glycine inhibits *L. monocytogenes* in a particular agar medium (Lee et al. at page 1215, left-hand column, second full paragraph). Neamatallah et al., as described above, teach that *L. monocytogenes* is resistant to sulphamethizole alone but that inclusion of sulphamethizole with colistin sulphate and nalidixic acid decreases growth of *L. monocytogenes* by an order of magnitude. Because certain combinations can unexpectedly decrease the growth of *L. monocytogenes*, each potential combination would have to be tested to assess its efficacy. Given the 24 different options and assuming that the options would be selected in groups of at least 14 (the recited number of ingredients), at least 2,000,000 different combinations are possible from the ingredients provided in the prior art.[1] This number of combinations is an underestimate as it excludes any further options regarding differences in concentration among the ingredients.

Of all the particular media described in the prior art, the Oxford Medium Base with the Oxford Antimicrobic Supplement (hereinafter, "Supplemented Oxford Medium") appears to be the closest to the medium recited in Claim 31. To arrive at the recited medium from the Supplemented Oxford Medium, a practitioner in the art would have to at least add tryptone, peptone, anhydrous dibasic potassium phosphate, yeast extract, naladixic acid, ceftazidime, and nitrofurantoin. A practitioner in the art would additionally have to decrease the lithium chloride concentration by a factor of 3 (from 15 g/L to 5 g/L), decrease the colistin sulfate (polymyxin E) concentration by a factor of 2 (from 20 mg/L to 10 mg/L), decrease the cycloheximide concentration by a factor of 8 (from 400 mg/L to 50 mg/L), increase the phosphomycin concentration by a factor of 4 (from 10 mg/L to 40 mg/L), and decrease the concentration from that taught by Neamatallah et al. by a factor of 8 (from 50 mg/L to 6 mg/L). Together, these differences constitute at least 12 independent changes from the Supplemented Oxford Medium. Assessing the effect of these 12 changes from the Supplemented Oxford Medium, taken either individually or in different combinations would involve at least 4,095 experiments.[2] This number of experiments is an

[1] This number was calculated with the calculator provided at http://www.mathsisfun.com/combinatorics/combinations-permutations-calculator.html.

[2] The number of experiments includes 12 experiments for each change taken individually, 66 experiments for 2 of the 12 changes in each possible combination, 220 experiments for 3 of the 12 changes in each possible combination, 495 experiments for 4 of the 12 changes each possible combination, 792 experiments for 5 of the 12 changes in each possible combination, 924 experiments for 6 of the 12 changes in each possible combination, 792 experiments for 7 of the 12 changes in each possible combination, 495 experiments for 8 of the 12 changes in each possible

underestimate as it excludes possible combinations of the other ingredients and concentrations described in the prior art.

Thus, the prior art does not teach a finite number of identified, predictable solutions for a *Listeria spp.*-selective medium that renders the medium recited in Claim 31 obvious.

In view of the foregoing, Claims 1-13, 15, 25-27, and 29-31 are not obvious over the cited prior art. Withdrawal of this rejection is requested.

Claims 16-24 and 28

Claims 16-24 and 28 depend from Claim 15. Claims 16-24 are each patentable over the cited prior art at least for the reasons stated above for Claim 15.

Notice of allowability of Claims 16-24 and 28 is requested.

New Claims

Claims 32, 33, and 34 depend from Claims 1, 15, and 31, respectively, and recite that the medium is substantially devoid of acriflavin. Claim 32 further recites that the medium further includes cycloheximide. Claims 32-34 are patentable over the cited prior art at least for the reasons stated above for Claims 1, 15 and 31. Additionally, each of Claims 32-34 recites a combination of cycloheximide in a medium substantially devoid of acriflavin. The prior art, however, teaches cycloheximide only in a medium that also includes acriflavin. Further, the prior art does not describe any properties of either cycloheximide or acriflavine that would prompt a practitioner in the art to include the former without the latter in a selective medium for *Listeria spp.* For these reasons, Claims 32-34 are patentable over the cited prior art.

Notification of allowability of Claims 32-34 is requested.

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combination, 220 experiments for 9 of the 12 changes in each possible combination, 66 experiments for 10 of the 12 changes in each possible combination, 12 experiments for 11 of the 12 changes in each possible combination, and 1 experiment for all 12 changes taken at once. These numbers were calculated with the calculator provided at http://www.mathsisfun.com/combinatorics/combinations-permutations-calculator.html.

CONCLUSION

Applicant submits the application is in condition for allowance. Early notification of such action is earnestly solicited.

The undersigned agent respectfully requests the Examiner to contact him if the Examiner has any questions regarding the application or the claims that arise. Telephone calls related to this application are welcomed and encouraged, specifically if the telephone calls facilitate allowance of the application. The Commissioner is authorized to charge any fees or credit any overpayments relating to this application to deposit account number 18-2055.

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I certify that this paper is being electronically submitted to the U.S. Patent and Trademark Office via the EFS-Web system on the following date:

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